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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,254	04/09/2004	Shahriar Shane Taremi	JB06017US01	1701

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SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

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04/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/822,254	TAREMI ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,14,15,28,30 and 34-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *14,28,30,34 and 35* is/are allowed.

6)☒ Claim(s) *1,2,15 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-2, 14-15, 28, 30, and 34-39 are pending in the application.

[2] Applicant's amendment to the claims, filed on 2/26/08, is acknowledged. Claims 1-2, 14-15, 28, and 30 are amended relative to the claims filed on 9/6/07. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 2/26/08, is acknowledged.

[4] Applicant's arguments filed on 2/26/08 in response to the Office action filed on 10/26/07 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

[6] The objection to the specification as disclosing compounds at p. 38 with improper valencies for nitrogen and oxygen is withdrawn in view of applicant's instant specification amendment.

Claim Objection

[7] The objection to claims 1, 14, 28, and 30 because the nitrogens of the recited compounds have improper valencies is withdrawn in view of the instant claim amendment.

Claim Rejections - 35 USC § 112, First Paragraph

[8] The written description rejection of claims 14, 28, 30, and 34-35 under 35 U.S.C. 112, first paragraph, is withdrawn upon further consideration of the rejection and in view of applicant's accompanying remarks at the paragraph bridging pp. 11-12.

According to applicant's remarks, one of skill "would not consider these formulae as describing genuses because variable substituents are not included". Indeed, the recited compounds have no variable substituents and in view of applicant's remarks are interpreted as being a species rather than a genus of compounds that are exemplified by the recited formulae. Here, the phrase "represented by" in claims 14, 28 (claim 34 dependent therefrom), and 30 (claim 35 dependent therefrom) has been interpreted as meaning that the recited formulae represent a physical, tangible compound, which is limited to the recited formula.

[9] The written description rejection of claims 1-2, 15, and 36-39 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 13 beginning at p. 5 of the Office action filed on 10/26/07.

RESPONSE TO ARGUMENT: Addressing the examiner's interpretation of claims 1-2, 15, and 36-39 as encompassing crystalline forms of the polypeptide or polypeptide-compound complex, applicant agrees with the examiner's noted interpretation, however, argues against the examiner's position that the genus of polypeptides in crystalline form are not adequately described. Specifically, applicant argues that description of the amino acid sequence of the polypeptide is sufficient to describe a genus of crystals of that polypeptide, citing *Fiers v. Revel, Regents of the University of California v. Eli Lilly and Co.,* and *Invitrogen Corp. v. Clontech Labs., Inc.* According to applicant, limiting the claims to being "non-crystalline" to satisfy the written description requirement would "not be justified" and that "the instant claims should not need to be so limited in order to comply with the written description requirement".

Applicant's argument is not found persuasive. According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)." In the instant response, applicant confirms the examiner's broad, but reasonable interpretation of the claims as encompassing polypeptides and polypeptide-compound complexes in crystalline form. Thus, the examiner must not only consider analyze the genus of non-crystalline polypeptides and polypeptide-compound complexes for adequate written description, but must also analyze the genus of *crystalline*

polypeptides and polypeptide-compound complexes for adequate written description. The examiner maintains the position that such crystalline polypeptides and polypeptide-compound complexes are not adequately described by the instant specification.

The examiner acknowledges the respective Court's holding in *Fiers v. Revel, Regents of the University of California v. Eli Lilly and Co.,* and *Invitrogen Corp. v. Clontech Labs., Inc.* and it is noted that the examiner's position is not in conflict with the finding of adequate written description in each of these cases, particularly as the respective Court does not appear to have dealt with the issue of *crystalline* polypeptides or polypeptide-compound complexes. Here, it is not the non-crystalline polypeptides *per se* that are at issue, rather it is the *crystalline forms* of the polypeptides or polypeptide-compound complexes that lack adequate written description.

Applicant appears to take the position that since the specification discloses the amino acid sequences of SEQ ID NO:6, 8, 10, and 12 and the compounds as recited in, *e.g.,* claim 1, then the specification necessarily provides adequate written description for all crystalline forms thereof. Put another way, applicant takes the position that the amino acid sequence of SEQ ID NO:6, 8, 10, and 12 and the recited compounds is sufficient to show possession of all crystals thereof. However, it is noted that other than a single species of crystal of SEQ ID NO:10 having characteristics as recited in claim 28 and a single crystal of SEQ ID NO:6 having characteristics as recited in claim 30, the specification fails to disclose any other representative species of the genus. Notably, the specification fails to disclose even a single representative species of the genus of crystals of SEQ ID NO:8 or 12. Applicant may argue that these single species are

representative of the entire genus, *e.g.,* one may apply the method of making the crystal of SEQ ID NO:10 to making a crystal of SEQ ID NO:8. However, it was well-known at the time of the invention that making crystalline polypeptides was highly unpredictable and that a method for successfully crystallizing a first polypeptide may not be applicable to a second polypeptide, which is undisputed by applicant. See the relevant teachings of Kierzek et al., Buts et al., and Branden et al. (cited in the PTO-892s filed on 8/8/06 and 8/26/05).

Even though the skill in the art is extremely high, even for those that are graced by being assisted with the latest technologies such as automated robotics, the art of crystallography is still rooted in trial-and-error procedures (see Abstract, Kundrot et al. *Cell. Mol. Life Sci.* 2004, 61: 525-536) and currently there are no directed methods which makes this process any easier or more predictable. Thus, each protein that is to be crystallized needs to be treated as its own entity possessing its own unique biochemical crystallization parameters which cannot be inferred or learned from other crystallized proteins.

The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a protein complex and vice-versa which may even contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein) complex (see also Weber, *Methods in Enzymology*, 1997, Vol. 276, pp. 13-22). At best, the art of

crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a role in obtaining crystallization conditions despite the extremely high skill level of those in the art (see Cudney, *Rigaku Journal*, 1999, Vol. 16, No. 1, pp. 1-7).

McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990) teaches (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids." Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to

elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual."

As noted above, the specification discloses only a single representative species of a crystal of SEQ ID NO:10 or 6 and fails to disclosed even a single representative species of a crystal of SEQ ID NO:8 or 12. Moreover, as noted above, the art of crystallography is *highly* unpredictable as evidenced by the cited references and which is undisputed by applicant. As noted in MPEP 2163, "For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

Applicant cites to Example 13 of the Written Description Guidelines, Example 1 of Trilateral Project B3b, and Case 5 of the Annex to Trilateral Project WM4 as further supporting the position that that since the specification discloses the amino acid sequences of SEQ ID NO:6, 8, 10, and 12 and compounds, the specification necessarily provides adequate written description for all crystalline forms thereof. Citing the interview summaries filed on 6/27/07, applicant argues that while the examiner has indicated that there is no evidence that Example 13 of the Guidelines or Case 5 of Trilateral Report WM4 were meant to encompass polypeptides, this is refuted by

USPTO comments in the Guidelines and Trilateral Report. Applicant argues that because Case 5 mentions protein crystallography, the polypeptide claim is clearly meant to encompass crystalline forms thereof and to exclude crystalline forms from the polypeptide claims of the cited case law would be contrary to claim construction law and USPTO policy. Applicant argues that even though the examiner has discussed this written description issue with a TC1600 TQAS and this policy was presented at a BCP meeting, “exactly what was stated at these events was not made of record and cannot fairly be used as any grounds on which to base any claim rejection". Applicant further argues the examiner’s assertion that the Written Description Guidelines “need not necessarily be followed in every case...was not committed to writing” and that to deviate from the Guidelines "would be improper".

Applicant’s argument is not found persuasive. In *Ex Parte Kubin,* Appeal 2007-0819 (BPAI 2007), the appellant relied on Example 14 of the Written Description Guidelines. The BPAI held that “With respect to Appellants’ reliance on hypothetical Example 14 in the Office’s *Synopsis*, “[c]ompliance with the written description requirement is essentially a fact-based inquiry that will ‘necessarily vary depending on the nature of the invention claimed.’ *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) (quoting *In re DiLeone*, 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971)), *quoted with approval in Enzo*, 323 F.3d at 963, 63 USPQ2d at 1612. While the *Written Description Guidelines* and the hypothetical examples in the Office’s *Synopsis* can be helpful in understanding how to apply the relevant law (as it existed in 2001 when the Guidelines were adopted), they do not

create a rigid test". Similarly, while applicant relies on the Written Description Guidelines and Trilateral Reports B3b and WM4, these are not meant to create a rigid test of patentability, particularly as the analysis of written description under 35 U.S.C. 112, first paragraph, is based upon the facts of each case. While applicant argues the examiner has improperly excluded polypeptide crystals as being encompassed from the claims of the case law, there is no evidence of record or line of reasoning that the claims of the cited case law were intended as encompassing crystalline forms of the polypeptide. In view of the broad, but reasonable interpretation of the claims as encompassing crystals and the high level of unpredictability in making protein crystals and their resulting properties, which is undisputed by applicant, it is the examiner's position that the specification fails to adequately describe all crystalline forms of SEQ ID NO:6, 8, 10, and 12 and complexes thereof such that a skilled artisan would recognize that applicant was in possession of all members of the claimed genus.

[10] The scope of enablement rejection of claims 14, 28, 30, and 34-35 under 35 U.S.C. 112, first paragraph, is withdrawn upon further consideration of the rejection and in view of applicant's accompanying remarks at the paragraph bridging pp. 11-12.

According to applicant's remarks, one of skill "would not consider these formulae as describing genuses because variable substituents are not included". Indeed, the recited compounds have no variable substituents and in view of applicant's remarks are interpreted as being a species rather than a genus of compounds that are exemplified by the recited formulae. Here, the phrase "represented by" in claims 14, 28 (claim 34

dependent therefrom), and 30 (claim 35 dependent therefrom) has been interpreted as meaning that the recited formulae represent a physical, tangible compound limited to the recited formulae.

[11] The scope of enablement rejection of claims 1-2, 15, and 36-39 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons set forth below. The rejection was fully explained in a prior Office action. See particularly paragraph 14 beginning at p. 7 of the Office action filed on 10/26/07.

RESPONSE TO ARGUMENT: Beginning at p. 21 of the instant remarks, applicant argues “The enablement requirement, with respect to a polypeptide, is met by description of the amino acid sequence of the polypeptide" and "This is regardless of whether the specification discusses crystals”. Applicant argues a skilled artisan could use the disclosed working examples to make any crystal as encompassed by the claims and even if the specification fails to enable all subject matter encompassed by the claims, the enablement provided by the specification still bears a reasonable correlation with the scope of the claims. According to applicant, the examiner is “giving undue weight to the number of crystals…while ignoring the other embodiments which are also encompassed”. Applicant points to Case 5 of the annex of Trilateral Report WM4, Example 5E of the Enablement Training Materials, and MPEP 2164.08 as supporting the position that all crystalline polypeptides as encompassed claims are fully enabled by the specification.

Applicant's argument is not found persuasive. Regarding applicant's reference to Case 5 of the annex of Trilateral Report WM4 and Example 5E of the Enablement Training Materials, as noted above, The BPAI has held that "With respect to Appellants' reliance on hypothetical Example 14 in the Office's *Synopsis*, "[c]ompliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.' *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) (quoting *In re DiLeone*, 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971)), *quoted with approval in Enzo*, 323 F.3d at 963, 63 USPQ2d at 1612. While the *Written Description Guidelines* and the hypothetical examples in the Office's *Synopsis* can be helpful in understanding how to apply the relevant law (as it existed in 2001 when the Guidelines were adopted), they do not create a rigid test". Similarly, while applicant relies on Case 5 of the annex of Trilateral Report WM4 and Example 5E of the Enablement Training Materials, these are not meant to create a rigid test of patentability, particularly as the analysis of enablement under 35 U.S.C. 112, first paragraph, is based upon the facts of each case. In view of the broad, but reasonable interpretation of the claims as encompassing crystals and the high level of unpredictability in making protein crystals and their resulting properties, which is undisputed by applicant, it is the examiner's position that the specification fails to fully enable all crystalline forms of SEQ ID NO:6, 8, 10, and 12 and complexes thereof as encompassed by the claims.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498,

504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims…and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims…claims are to be given their broadest reasonable interpretation that is consistent with the specification."

As acknowledged by applicant, claims 1-2, 15, and 36-39 encompass crystals of the polypeptide SEQ ID NO:6, 8, 10, or 12 and polypeptide-compound complexes. The crystals of the polypeptide are unlimited with respect to their characteristics, *e.g.,* space group and unit cell dimensions.

The broad scope of claimed crystals and crystallizable compositions is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of crystals as broadly encompassed by the claims. In this case the disclosure is limited to the crystals as set forth in claims 28 and 30. Applicant appears to take the position that the specification need not enable the full scope of the claims, particularly protein crystals, arguing the examiner is giving "undue weight" to the crystals encompassed by the claims while ignoring the non-crystalline subject matter. However, as noted by the Federal Circuit, "the specification must teach those skilled in the art how to make and use the *full* scope of the claimed invention without undue experimentation" (emphasis added). *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). While applicant cites MPEP 2164.08 and asserts the enabled two working examples and non-crystalline polypeptides are reasonably correlated with the scope of the claims, making and using non-crystalline polypeptides of the claims is *not* reasonably correlated with making and using protein crystals. Such is clearly born out by the state of the art regarding making crystalline polypeptides as discussed in detail below.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses two working examples of crystalline polypeptides. See particularly Example 2 beginning at p. 45 and Example 3 beginning at p. 63 of the specification. However, these working examples fail to provide the necessary guidance for making the entire scope of polypeptide and polypeptide-compound crystals as broadly encompassed by the claims. For example, the specification fails to provide

guidance for crystallizing the polypeptides of SEQ ID NO:8 and 12 or for example, SEQ ID NO:6 and 10 with additional amino acids at the N- and/or C-terminus.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The state of the art at the time of the invention acknowledges a high level of unpredictability for making a protein crystal. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999; cited in the PTO-892 filed on 8/26/05) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "The first prerequisite for solving the three-dimensional structure of a protein by x-ray crystallography is a well-ordered crystal that will diffract x-rays strongly…[w]ell-ordered crystals…are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1999) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline

added for emphasis, p. 2, left column, top). Also, Wiencek (*Ann Rev Biomed Eng* 1:505-534) teaches that "[p]rotein solubility will change dramatically as pH is altered by ~ 0.5 pH units…some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). See also the teachings of McPherson et al. (*supra*).

Additionally, Buts et al. (*Acta Cryst* D61:1149-1159, 2005) teaches that "Since the introduction of structural genomics, the protein has been recognized as the most important variable in crystallization." "Five naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging between 2.4 and 1.1 Å resolution." Specifically, the reference of Buts *et* al. teaches that the F17e-G and F17f-G adhesins differ in only one amino acid from the F17c-G adhesin, Arg21Ser and His36Tyr, respectively, and yet these proteins that are 99% identical in sequence resulted in different crystal forms with distinct diffraction properties (see Tables 1-3).

Skarzynski et al. (Acta Cryst D62:102-107, 2006) teaches "crystals of complexes obtained by compound soaking may become damaged, change their diffraction properties or even change the space group during the soaking experiment!" (p. 103, right column, middle). Skarzynski et al. further teaches that binding of potent compounds during soaking often causes complete or partial disruption of the crystal lattice, poorly soluble compounds may interfere with the diffraction pattern of the protein crystal sample, and very often no binding is observed for active compounds, despite

their potency under biochemical or biological assay conditions" (p. 104, left column, middle). The teachings of Skarzynski et al. are supported by applicant's specification, which teaches "Attempts to soak the GDP-4-keto, 6-deoxy mannose substrate or GDP into the crystals failed" (p. 15, top).

Even though the skill in the art is extremely high, even for those that are graced by being assisted with the latest technologies such as automated robotics, the art of crystallography is still rooted in trial-and-error procedures (see Abstract, Kundrot et al. Cell. Mol. Life Sci. 2004, 61: 525-536) and currently there are no directed methods which makes this process any easier or more predictable. Thus, each protein that is to be crystallized needs to be treated as its own entity possessing its own unique biochemical crystallization parameters which cannot be inferred or learned from other crystallized proteins.

The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a protein complex and vice-versa which may even contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein) complex (see also Weber, Methods in Enzymology, 1997, Vol. 276, pp. 13-22). At best, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two

conditions that are successful – if any at all. It is even a well-known fact in the art that luck often times play a role in obtaining crystallization conditions despite the extremely high skill level of those in the art (see Drenth, *supra,* Cudney, *Rigaku Journal*, 1999, Vol. 16, No. 1, pp. 1-7).

McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990) teaches (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids." Table 2 is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein.

The specific component and condition must be carefully deduced and refined for each individual."

Thus, in view of these teachings, a skilled artisan would recognize there is a high level of unpredictability in making a protein crystal.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallography were known at the time of the invention and the specification discloses two working examples thereof, it was not routine in the art to screen all polypeptides, in apo-form or optionally in complex with any compound as encompassed by the claims for those that will yield diffraction-quality crystals.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is

unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

[12] Status of the claims:

- Claims 1-2, 14-15, 28, 30, and 34-39 are pending.
- Claims 1-2, 15, and 36-39 are rejected.
- Claims 14, 28, 30, and 34-35 appear to be in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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